This document was developed by NIEHS/NTP staff to facilitate internal and external review of a proposed research program prior to designing and conducting toxicology studies. The purpose of the research concept document is to outline the general elements of a research program that would address the specific public health concerns that prompted the nomination of the substance or issue for study. It may also encompass substance-specific studies that address larger public health issues or topics in toxicology. Additional information about the nomination, review, and selection of substances for study by the NTP is provided at ***Nominations to the NTP Testing Program*** (*http://ntp.niehs.nih.gov/go/nom*). A draft version of this research concept was reviewed by the NTP Board of Scientific Counselors at a public meeting on June 11-12, 2008 (*http://ntp.niehs.nih.gov/go/9741*) and subsequently approved by the NTP Executive Committee.

NTP Research Concept: 2,2'-Dimorpholinodiethyl Ether

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Nomination Rationale and Background

2,2'-Dimorpholinodiethyl ether (DMDEE) is a specialty amine catalyst used in the production of flexible foam, high-resilient (HR) molded foam, and in coatings and adhesives. Although its production exceeded 1 million pounds in 1998 and 2002 it does not meet the criteria for inclusion in the EPA HPV Challenge Program. Because of the lack of data on the toxicology of DMDEE and the significant potential for human exposure, DMDEE was nominated by the National Cancer Institute (NCI) for evaluation (http://ntp.niehs.nih.gov/go/32744). Specifically, the nomination requested initial toxicological characterization and determination of whether or not N-nitrosomorpholine, a well known hepatocarcinogen, is formed from DMDEE as a result of metabolic transformation.

DMDEE is also used as a catalyst in polyurethane insulating foams released under pressure or from pressurized cans, in hot melt urethane adhesives, in the formation of flexible orthopedic casts, and in warm melt adhesives used in book binding applications. The primary source of exposure to DMDEE would be expected to occur in the workplace during the manufacture of slabstock flexible foam, HR molded foam, hot melt adhesives, and possibly other products. During the initial phase of foam rise there is a blow-off of chemicals from the foam so the first stage of the continuous foaming process is done in an enclosed ventilated area. However, directly after this stage, the foam is cut and moved along conveyors to a storage area; during this phase plant workers are exposed to any vapors emitted from the cut foam. Moreover, during application of hot melt adhesives at elevated temperatures, fugitive catalyst can escape from the adhesive. In addition to the environmental problems created, the loss of catalyst makes the curing rate less consistent. This is particularly pronounced in open roll coater applications where the adhesives are constantly exposed to high temperatures and a strong, open ventilation air flow. Additional workers may be exposed to unreacted catalyst while preparing final products from plastics and foams being machined into final products. Slabstock foam products are primarily used in furniture seat cushions and bedding materials; molded foam is used in automotive seats, packaging, and a wide range of specialty products.

There is no information on the toxicology of DMDEE in the published literature. The Material Safety Data Sheet lists DMDEE as a skin, eye, and respiratory irritant, and lists an oral LD_{50} of greater than 2000 mg/kg in the rat suggesting that it is not acutely toxic. It is also listed as poorly biodegradable. It is miscible with water, freezes at -280 ^{0}C, boils above 320 ^{0}C, and has a low vapor pressure (0.578 mm Hg at 123 ^{0}C). DMDEE has a pH = 10.4, which may be the basis of its

irritant properties.

Key Issues

The key issue addressed in this concept proposal is a complete examination of the absorption, distribution, metabolism, and elimination of DMDEE with specific monitoring for formation of N-nitrosomorpholine during the metabolism of DMDEE. Metabolic formation of N-nitrosomorpholine would indicate a significant hazard associated with exposure to DMDEE. The mutagenicity of DMDEE will also be examined since N-nitrosomorpholine is a bacterial mutagen and induces DNA strand breaks in mammalian cells *in vitro*.

The major routes of exposure to DMDEE are dermal and perhaps inhalation of aerosol containing DMDEE; the low vapor pressure of DMDEE makes it unlikely that there would be significant exposure to DMDEE vapor.

Proposed Approach

Absorption, distribution, metabolism, and elimination studies will be conducted by the oral and dermal routes of exposure with monitoring for the formation of N-nitrosomorpholine. N-nitrosomorpholine can be detected by the presence of N-nitroso(2-hydroxyethyl)glycine, the major metabolite of N-nitrosomorpholine, in the urine of animals exposed to DMDEE. The mutagenicity of DMDEE will be examined in bacteria and DNA reactivity examined in mammalian cells.

Significance and Expected Outcome

DMDEE is a high production volume chemical with wide use in the manufacture of a number of products and significant potential for occupational exposure. If N-nitrosomorpholine is formed as a by-product of metabolism then occupational exposure to DMDEE must be greatly minimized and the possibility of consumer exposure must be carefully examined.

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